REMARKS

Claim Amendments

The typing errors corrected in the definitions of R^3 and R^4 in claim 1 in the last Reply were inadvertently not corrected properly. They are now corrected. The same corrections are also made in claim 19. Support for the corrections can be found, for example, on page 1, lines18-27 of the specification and also in original claim 1.

The First Rejection Under 35 USC § 112, first paragraph

The Office Action alleges that the formation of solvates is not enabled because, e.g., the formation of solvates is unpredictable. In support, the Office Action quotes a passage from *Vippagunta* which indicates that certain predictions about solvates or hydrates of a compound are complex and difficult.

However, the Office Action appears to ignore within the same document the passages which show the claims are enabled. For example, *Vippagunta* on page 15, top of first column, states that

> It has been established that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. (Emphasis added.)

Likewise, the abstract of *Vippagunta* starts with the statement that

> Many drugs exist in the crystalline solid state due to reasons of stability and ease of handling ... Crystalline solids can exist in the form of polymorphs, solvates or hydrates. (Emphasis added.)

Also on page 4, first paragraph, *Vippagunta* states that

> Most organic and inorganic compounds of pharmaceutical relevance can exist in one or more crystalline forms. ...
>
> The common crystalline forms found for a given drug substance are polymorphs and solvates. (Emphasis added.)

Moreover, *Vippagunta* throughout the reference teaches various solvates, hydrates, etc., structural aspects thereof, examples thereof, including preparation techniques, and methods/techniques for the characterization thereof. See, e.g., pages 15-18.

While it may be true, that the prediction of what a particular solvate of a compound will actually look like, e.g., whether one, 3 ½, 6 or 12 solvent molecules are incorporated, the Office Action is incorrect with respect to the alleged lack of enablement.

Even the very paper cited in support of the rejection demonstrates that one of ordinary skill in the art in the field of pharmaceuticals would know how to proceed in preparing solvates and how such solvates would be identified or characterized, e.g., by polarized light microscopy, etc. See extensive list of techniques identified on column 2 of page 18.

Additionally, based on the above discussed statistics in this field provided by *Vippagunta*, one of ordinary skill in the art would also have a good expectation for success. While certain predictions may be difficult in the art of forming solvates, the formation of solvates is common with pharmaceutically active ingredients and methods of detecting and characterizing them are well-known and widely applied routinely.

In sum, *Vippagunta*, rather than supporting a lack of enablement rejection, supports the opposite, i.e., that there is no lack of enablement.

Thus, the Office Action has not carried its burden in establishing a lack of enablement because the Office Action has not established any basis to doubt objective enablement. See *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (1971) holding that a specification disclosure which "contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (Emphasis added.) See also *In re Bundy*, 209 USPQ 48 (1981) holding that the "PTO must have adequate support for its challenge to the credibility of applicant's statements of utility," which statements were made in *Bundy* in the context of an enablement rejection, and which is lacking in the present case. In view of the state of the art, it is evident that there is no indication that one of ordinary skill in the art would have questioned that solvates could be formed. See *Rasmusson v. Smithkline Beecham Co.*, 75 USPQ2d 1297 (CA FC 2005).

Nevertheless, applicants provide further information clearly demonstrating that solvate formation is a common phenomenon among pharmaceutical substances, i.e., Polymorphism: in the pharmaceutical industry (edited by *Ralf Hilfiker*; 2006 Wiley-VCH), Chapter 8, The Importance of Solvates, by *U. J. Griesser*, pp. 211-222 (hereinafter *Griesser*).

On page 220, *Griesser* teaches that

> Over almost two decades we carefully collected data on the solid-state properties of a few thousand pharmaceutically relevant organic compounds, with special focus on those drug substances listed in the Pharmacopoeia European (PhEur). The

> 1997 edition of PhEur contained 559 well-defined organic drug compounds. ... For more than 55% of them either polymorphs or solvates are known. In a newer evaluation of a larger set of data (PhEur edition 4.02, 8008 solid organic compounds ... this fraction increased only slightly to 57%. As shown in Fig. 8.4, 29% of the compounds are known to form hydrates, 10% other solvates ... (Emphasis added.)

Additionally, various factors in considering whether solvates would be expected to form are identified by *Griesser* on pages 220-221, e.g., salt forms, molecular size, lipophilicity. A citation is provided for ascertaining "further trends and interrelations between molecular properties and solvate/hydrate formation." See the middle of page 221. All this demonstrates that one of ordinary skill in the art would know or have guidance as to what factors to consider in expectation of success.

Moreover, under the section titled "Generation and Characterization of Solvates" on page 222, *Griesser* teaches that

> Since it is imperative to establish the crystal forms of an active pharmaceutical ingredient (API) to satisfy the regulatory authorities ..., solvates of drug compounds are now preferentially discovered in systematic polymorph screenings. ... **Automated crystallization systems and strategies** have been developed to speed up this process, **allowing thousands of crystallization experiments in a short time**. (Emphasis added.)

In view of the state of the art of solvate formation, e.g., solvate formation being a very common phenomenon associated with drug substances, the generation and examination of which is done with highly automated machines, the Office Action has not established that it would require undue experimentation by one of ordinary skill in the art to prepare and even characterize the solvates of a compound.

While the amount of work to prepare solvates of the compounds of the invention may require some effort or maybe even considerable effort (although not admitted), no undue experimentation is required in the preparation of solvates. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988). One of ordinary skill in the art merely through routine laboratory efforts can take various compounds of the invention, which are explicitly admitted by the Office Action to be enabled at the top of page 3, bring them

together with various solvents and check whether solvates have formed. This type of work is merely routine laboratory work and does not require undue experimentation. Moreover, as discussed in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the "test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine," which it is in the present case.

Reconsideration is respectfully requested.

The Second Rejection Under 35 USC § 112, first paragraph

Applicants respectfully disagree with the rejection, but to advance prosecution to an expeditious allowance amended the application without prejudice or disclaimer to render moot the rejection.

Double Patenting Rejections – Substantial Duplicate Claims Allegations

Claim 19 was not a substantial duplicate of claim 1 and claim 21 is not a substantial duplicate of claim 7. For example, claims 1 and 7 recited and recite solvates while claims 19 and 21 did not and do not recite solvates.

Obviousness-Type Double Patenting Rejection

The obviousness-type double patenting rejection is not justified over copending US 10/551,998. There is no corresponding substituent in the compounds claimed in US '998 to the present claims' R^2 group, which denotes $(CH_2)_nHet$, $(CH_2)_nAr$, or cycloalkyl having 3 to 7 C atoms.

The Office Action points to a compound 6 on page 9 in the specification of US '998. Applicants do not see a compound 6 on said page. However, even if the allegation is correct, which is not admitted, such compound in the specification of US '998 is irrelevant to an obviousness-type double patenting rejection.

The claims of the present application are not obvious over the claims of US '998. And thus, there is no obviousness-type double patenting.

The First Rejection Under 35 USC § 102

The amendments render the rejection over US '445 moot.

The Second Rejection Under 35 USC § 102

The rejection over US '343 is not proper and was not proper even for the original claims because according to the invention, none of R^2 and R^4 can be CN.

The Rejection Under 35 USC § 103

The subject matter of WO '435 and the claimed invention of the present application were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person, whereby this rejection is moot.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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